NCI-Frederick
Animal Care & Use
March 2005

Newsletter Contents

ACUC Member Spotlight

Dr. Karlyne Reilly

Dr. Reilly received her Ph.D. in molecular and cellular biology from Harvard University in 1997 studying frog development in *Xenopus laevis*. After her work in frogs, she moved to the Center for Cancer Research at MIT to conduct genetic experiments in mouse models of cancer. In 2002, she established the Genetic Modifiers of Tumorigenesis section at the NCI-Frederick. Her laboratory focuses on using mouse models of human cancer to understand tumor biology and the role of genetic background on initiation and progression of tumors. Her group is looking at how naturally occurring polymorphisms affect tumorigenesis and how these polymorphisms interact with the mutations that accumulate during tumor initiation and progression. Dr. Reilly is focusing on mapping modifier genes for resistance to brain cancer and peripheral nerve cancer in different inbred strains of mice. By understanding why certain mouse strains are genetically resistant to developing brain cancer or peripheral nerve cancer, Dr. Reilly hopes to design new therapies against these tumors and develop ways to screen for high-risk patients, to aid in genetic counseling and to promote more effective early detection methods. In addition to her work on modifier genes, Dr. Reilly's group is developing the mouse model of brain cancer to better understand the signal transduction pathways important in tumorigenesis and to test experimental therapeutics that can block these pathways. Dr. Reilly joined the NCI-Frederick ACUC in 2003 to help promote the humane use of animals at NCI-Frederick to further biomedical research.

AAALAC International Site Visit

As mentioned in our last newsletter, the NCI-Frederick animal care and use program underwent its triennial site visit by the **Association for Assessment and Accreditation of Laboratory Animal Care International** on March 7 and 8, 2005. Below is a note from Dr. Craig Reynolds in regards to this site visit:

It is with great pleasure that I announce to you that our animal program will be recommended for "Full and Continued Accreditation" … the highest recommendation that can be received! The site visit team was extremely complementary of all the areas in support of the NCI-Frederick lab animal program. I would like to share with you some of the praise that they gave to all of you:

The entire LASP staff did a wonderful job participating in the site visit process. Everyone interacted with the site visit team in a confident and well-informed manner. It was evident to the team that the LASP staff was highly dedicated, well-trained and provided excellent care to the animals. In addition, they noted that there were excellent lines of communication throughout the LASP.

Moreover, both the LASP and FME were commended for the high quality of care that was provided to all the animals in such well-maintained buildings. The team was particularly impressed by this considering the advanced age of the buildings. The site visitors felt that this was evidence of the commitment of both the LASP and FME to work together to provide the best possible program within "less than ideal" physical facilities.

The site visit team went on to praise the efforts of the Animal Care and Use Committee regarding establishment of animal care and use guidelines, excellent communication with the scientific staff, sound review of Animal Study Proposals and ensuring that study proposals were properly implemented.

It is clear to me that it was the integrated efforts of the LASP, FME and ACUC that has resulted in such a positive site visit recommendation. Furthermore, I firmly believe that because of your daily dedication to this program, you have provided the NCI-Frederick with an outstanding animal research program not only during this site visit process, but more importantly, on a continuing long-term basis.

Congratulations on a job well done!

NCI-Frederick Animal Care and Use Links

Home Page
Guidelines and Recommendations
Alternatives
Training
Forms

The ACUC is always interested in new members to assist the committee. If you are willing to volunteer as an ACUC member or to participate in any of its subcommittees, please contact the NCI-Frederick ACUC Office

Regulations and Policies Links

Animal Welfare Act
Public Health Service Policy
Guide for the Care and Use of Laboratory Animals
U.S. Government Principles

NCI-Frederick Animal Care & Use
March 2005

New/Revised ACUC Policies and Recommendations

The ACUC has recently adapted the following new and revised guidelines and recommendations. Please ensure that you and your staff review these guidelines and incorporate as they apply to your research study.

- *Guidelines for Survival Bleeding of Mice and Rats*
- *Guidelines on Tail Biopsy for DNA Analysis/Genotyping*
- *Investigating and Reporting Animal Care and Use Concerns*
- *Guidelines for the Use of Tribromethanol/Avertin Anesthesia*
- *Recommendations for Aseptic Technique and Post-Operative Care*

These guidelines can be found at the following site: **http://web.ncifcrf.gov/rtp/lasp/intra/acuc/fred/guidelines_nci.asp**

Animal Care and Use Training Initiatives

The NCI-Frederick Animal Care and Use Committee and the Laboratory Animal Sciences Program focus on a variety of training sessions throughout the year to ensure that individuals are educated on the responsibilities involved with the humane care and use of animals, the appropriate handling of rodents, as well as the identification and reporting of animal health conditions. Here is a listing of current training courses that are offered:

- *The Care and Use of Animals in Laboratory Research Lecture Course (ACUC)*
- *Animal Care and Use Introductory Online Training Course for New Employees (ACUC)*
- *Animal Care and Use Committee Member Training Course (ACUC)*
- *New Employee Orientation "Animal Use in Biomedical Research" Lecture Training Course – available in various languages (LASP)*

The ACUC and LASP will be launching the following training initiatives this year:

- *Animal Care and Use Refresher Online Training Course (ACUC)*
- *Online New Employee Orientation Training Course (LASP)*
- *Dermatology Training Module (LASP)*
- *Animal Health Photo Library (LASP)*
- *Overview of Animal Care and Use Guidelines for Animal Care and Technical Staff (LASP)*

Please contact the **ACUC Office** for additional information on any of these training initiatives.

Humane Endpoints Database

During the Animal Study Proposal review process, the Animal Care and Use Committee is responsible for ensuring that humane endpoints are built into an investigator's experimental design. An endpoint may be defined as "the point at which an experimental animal's pain and/or distress is terminated, minimized, or reduced by taking actions such as killing the animal humanely, terminating a painful procedure, or giving treatment to relieve pain and/or distress." Animals are not permitted to experience unalleviated pain or distress as a result of proposed procedures unless scientifically justified and approved by the ACUC in advance. In an effort to assist investigators in identifying the earliest endpoint that is compatible with the scientific objectives of their research, the Alternatives to Animal Testing Web Site (**ALTWEB**) has developed a humane endpoints database. The ACUC encourages investigators to utilize this site when preparing experimental proposals that may involve painful procedures.

- *From the Canadian Council on Animal Care (CCAC) Guidelines on Choosing an Appropriate Endpoint in Experiments Using Animals in Research Teaching and Testing (1998)* ***http://www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/GDLINES/ENDPTS/APPOPEN.HTM.***

Recombinant DNA in Animal Models

As mentioned in a previous newsletter, the NCI-Frederick ACUC and Institutional Biosafety Committee have worked together to ensure that adequate information regarding the use of transgenic and knockout animal models *(Section B1 of the NCI-Frederick Animal Study Proposal Form)* is provided to address potential health threats to humans working with these animal models.

There are several important issues to consider when assessing the potential hazards associated with introducing recombinant DNA into an animal for research purposes. It is essential that the people doing the experiments (1) know what recombinant DNA sequences are present in the animals and/or cells used in the experiments they are conducting; (2) that all the people who are directly involved with the animals, cells and/or tissues that derive from the experiments have a clear idea of what they are working with; and (3) if there are any potential risks associated with the work. The most important consideration is whether there is the potential for part or all of the recombinant DNA to be transmitted to other animals and/or humans. In general, the fundamental issue is whether part or all of the recombinant DNA can be mobilized as a virus either

NCI-Frederick Animal Care and Use Links

Home Page
Guidelines and Recommendations
Alternatives
Training
Forms

The ACUC is always interested in new members to assist the committee. If you are willing to volunteer as an ACUC member or to participate in any of its subcommittees, please contact the **NCI-Frederick ACUC Office**

Regulations and Policies Links

Animal Welfare Act
Public Health Service Policy
Guide for the Care and Use of Laboratory Animals
U.S. Government Principles

NCI-Frederick Animal Care & Use
March 2005

by itself or by some interaction (complementation and/or recombination) with other viruses, viral vectors or viral segments (either endogenous or exogenous) present in any cells that contact the recombinant DNA in the course of the experiment and the impact this may have for the animal host and/or the humans that interact/care for the animals. If the possibility exists that recombinant DNA can be mobilized, it is also important to consider whether the resulting virus might be potentially pathogenic to the host animals or to humans. With these considerations in mind, the safest experiments involve the introduction of DNA sequences (either directly into the animal or into cells that will be introduced into the animal) that contain no viral sequences. There is little reason to expect DNAs of this type to be mobilized so there is little or no risk. In contrast, experiments with viral sequences and/or viral vectors need more careful consideration.

Overview of possible risks associated with viral elements in animal experiments

- Experiments with minimal DNA segments from viruses that do not normally infect the animal used in the experiments (CMV promoters in mouse cells/mice for example). Although there is some remote possibility that this could lead to recombination, it is unlikely that recombination will occur if such viral promoters are used in mice or other non-primate hosts.
- Experiments that involve minimal DNA segments from viruses that can infect the animal host. The issue here is whether there is any reasonable expectation that the animal host has an endogenous complementing virus or will be infected with a complementing virus. It is particularly important, if the viral sequences are from a retrovirus, to consider the possibility of recombination of a retroviral promoter with a related endogenous virus (for example when a murine LTR promoter is used to express a gene in a mouse or in mouse cells).
- Experiments involving replication-defective or replication-incompetent viral vectors. In planning experiments with viral vectors that are intended to be defective, it is important to consider the possibility of the experimental protocol giving rise to replication competent recombinants. This is obviously an issue with the defective adenovirus vectors that are rendered replication incompetent through the deletions of E1a or E2, E3, and E4. Special consideration needs to be given to determining the possibility of an experiment giving rise to replication recombinants for experiments using retroviral vectors that are generated using complementing segments from a single viral parent or, whenever a retroviral vector is passed through cells that harbor closely related endogenous viruses (i.e. mouse retroviral vectors passed in murine cells). For instance, VSV-G can efficiently pseudotype retroviral vectors. VSV-G pseudotyped retroviral vectors have not been shown to generate replication competent recombinants provided the retroviral env gene has a substantial (non-reverting) deletion. It should be noted that the use of VSV-G will significantly expand the host range of the viral pseudotype. Additionally, it is also important to remember that the humans who prepare the vector stocks and/or care for the animals can carry viruses related to the vectors (human adenoviruses for example) and may serve as a source of complementing sequences.

Questions to consider when conducting experiments involving viral elements

- Can the resulting virus infect either other animals or humans? It is important to distinguish the generation of viruses that can infect the target animal (and humans) from those that cannot.
- If a virus is produced that can infect either animals or humans, will the resulting virus replicate or be replication defective? This is an important distinction: there are a number of viruses that will infect hosts but they will not replicate. For example the ASLV family of avian retroviruses can be modified so that they will infect mammalian cells; however, even when the mammalian cells are infected, ASLVs do not produce infectious viruses in human cells. ASLV-based vectors can be distinguished on this basis from viruses (like the murine retroviruses) that can replicate in mammalian cells (including human cells). Special care is always warranted when using viral vectors known to be replication competent and to infect a broad range of species, including humans (vaccinia vectors for example).
- Is the unmodified version of the vector known to be pathogenic in either animals or humans? Even though murine retroviral vectors can replicate in human cells, long experience has shown that these viruses do not set up active pathogenic infections in immunocompetent humans. Extra care must be taken with vector systems that are derived from known pathogens that can replicate in humans (like HIV-1).
- Has anything been done to the vector (inserted sequences, enhanced host range, etc.) that might increase its potential pathogenicity, or the potential pathogenicity of viruses (resulting from a recombination event) that could reasonably be expected to derive from the vector? Such experiments can be done safely, but extra care is needed, and careful thought should be given to the best way to minimize potential hazards of this sort.

A special thanks to Dr. Stephen Hughes and the NCI-Frederick Institutional Biosafety Committee for this contribution.

NCI-Frederick Animal Care & Use
March 2005

Material Transfer Agreements for the Transfer of Animals at NCI-Frederick

The new NIH "Policy for the Sharing of Model Organisms for Biomedical Research" (**http://www.nih.gov/science/models/**) became effective on October 1, 2004. This policy is an extension of the NIH general policy on sharing research resources, and reaffirms NIH's support for the timely sharing of animal models and other research tools developed with federal funds (**http://ott.od.nih.gov/RTguide_final.html**)

Whenever animals are transferred out of or into NIH by investigators under their own auspices, i.e., not through established procurement or repository mechanisms, such transfer must be documented by an NIH-approved material transfer agreement (MTA). This material transfer agreement may take many forms.

The preferred MTA for transferring animals into and out of NIH is the newly approved "Material Transfer Agreement for the Transfer of Model Organism (MTA-TO) to Academic and Non-Profit Agencies." Often the institution providing animals to NIH will send an agreement for signature before animals are transferred to NIH. This non-NIH agreement must be forwarded to the NCI Technology Transfer Branch (TTB) for appropriate review and approval. If no agreement is proffered by the outside provider, it is the responsibility of the NIH investigator to suggest that such an agreement be negotiated. Again, the preferred agreement is the MTA-TO. NCI-TTB is happy to assist investigators with executing such an MTA. Alternatively, most universities and other non-profit organizations are amenable to using the NIH Simple Letter Agreement (SLA) for providing animals to NIH. If the SLA is used to cover the transfer of animals into NIH, other terms may need to be included. For example the use of Cre-Lox or OncoMouse technology must be identified and the ownership of this technology by DuPont must be acknowledged. Permission to cross breed the animal model must be obtained if needed.

In summary, whenever an NIH investigator requests the transfer of animals into or out of the NIH, it is their responsibility to make sure a material transfer agreement is put in place to document such transfer if necessary.

The NCI TTB is available to assist all NCI-Frederick investigators with developing an appropriate material transfer agreement for each case. You may contact the NCI TTB at 301-846-5465 or **http://ttb.nci.nih.gov/.**

A special thanks to Ms. Donna Bialozor and Dr. Charmaine Richman of the NCI Technology Transfer Branch for this contribution.